

Cancer in Patients With Ataxia-Telangiectasia and in Their Relatives in the Nordic Countries

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Background: Epidemiologic studies of the families of patients with ataxia-telangiectasia (A-T), a recessive genetic neurologic disorder caused by mutation of the ATM gene, suggest that heterozygous carriers of an ATM mutation are at increased risk of cancer. A population-based study of cancer incidence in A-T families with unbiased selection and tracing of relatives would confirm this hypothesis. **Methods:** We conducted a study in the Nordic countries of 1218 blood relatives of 56 A-T patients from 50 families. The relatives were identified from population registries, and the occurrence of cancer was determined from cancer registry files in each country and compared with national incidence rates. All statistical tests were two-sided. **Results:** Among the 56 patients with A-T, we observed six cases of cancer (four leukemias and two non-Hodgkin's lymphomas) compared with 0.16 expected, yielding a standardized incidence ratio (SIR) of 37 (95% confidence interval [CI] = 13 to 80). Among the 1218 relatives, 150 cancers were recorded, with 126 expected (SIR = 1.19; 95% CI = 1.01 to 1.40). Invasive breast cancer occurred in 21 female relatives of A-T patients (SIR = 1.54; 95% CI = 0.95 to 2.36), including five of the 50 mothers (all of whom are obligate ATM mutation carriers) (SIR = 7.1; 95% CI = 2.3 to 17). Relatives who were less likely to be carriers of a mutant ATM allele had no increase or only a modest, statistically nonsignificant increase in the risk of breast cancer. There was no evidence of increased risk for cancer at any other site. **Conclusions:** We confirmed the previously recognized high risk of lymphoma and leukemia in A-T patients. Our data are also consistent with an increased risk of breast cancer among blood relatives of A-T patients. The epidemiologic findings suggest, however, that, even if ATM mutations are responsible for some breast cancer cases, ATM is a relatively weak genetic risk factor for the disease. [J Natl Cancer Inst 2001;93:121-7]

Ataxia-telangiectasia (A-T) is an autosomal recessive disease with an estimated frequency in the range of one per 40 000 to one per 300 000 births (1,2) that is caused by mutations of both alleles of the ATM (ataxia-telangiectasia, mutated) gene (3). A-T is an early-onset progressive neurologic disorder associated with a complex phenotype that includes cancer susceptibility, radiosensitivity, and immunodeficiency (4,5). Individuals with A-T have a 50-fold to 150-fold excess risk of cancer (6). Heterozygous carriers of an altered ATM allele appear to be clinically normal but are reported to be at increased risk of developing cancer, especially of the female breast (7-12), although the evidence to date is not entirely convincing (13,14).

Estimated frequencies of between 0.2% and 1% for hetero-

zygous carriers of an altered ATM allele in the general population suggest that, if heterozygosity for ATM is associated with breast cancer, it may be responsible for a sizable proportion of breast cancers in the (female) population (8). Thus, on the basis of the observed breast cancer incidence rates in adult blood relatives of patients with A-T in 110 families in the United States, Swift et al. (6) estimated in the late 1980s that some 7.5% of the breast cancers that occur in that population are attributable to heterozygosity for an ATM gene mutation. A more recent study by the same group using molecular genotyping (15) concluded that 6.6% of all breast cancers occur in ATM heterozygotes. In contrast, however, studies in France, Sweden, and Canada and another study in the United States found no association between ATM carrier status and breast cancer in women from families with breast cancer (16,17), in women aged 40 years or less at the time of diagnosis (18), or in women with sporadic breast cancer (19,20).

Thus, the question as to whether the ATM gene mutation in the heterozygous state could be a (breast) cancer susceptibility gene still requires clarification. Reliable evidence can come from cancer incidence studies of A-T patients and their relatives residing in countries with high-quality civil registration systems and population-based cancer registries, which can provide unbiased identification of patients and their relatives and determination of their cancers. Our study was initiated to test the hypothesis that blood relatives of patients with A-T are at increased risk of breast cancer. The risk of leukemia or lymphoma in relatives was another prior focus because these tumors occur frequently among A-T patients. Risk assessments of other types of cancers, however, were looked on as exploratory in nature.

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PATIENTS AND METHODS

In a collaborative study within the Nordic countries, the incidence of cancer was assessed in A-T patients and their blood relatives and compared with rates of cancer in the respective general populations. The total population of the Nordic countries was 23 million in 1990.

Identifying A-T Patients

In each country, pediatric neurologists, pediatric immunologists, medical geneticists, and the medical staff of cytogenetic laboratories and institutions for disabled children were requested to report cases of verified or suspected A-T (from 1950 through 1995) to the country's study coordinator. When we were unable to conduct clinical and biochemical examinations to verify the A-T cases, the relevant information from the medical records was obtained and reviewed. No case of A-T was identified in Iceland (population, 260 000).

The clinical and laboratory criteria used to categorize cases of A-T are shown in Table 1. A total of 56 patients within 50 families were included, each of whom was characterized by name, sex, and personal identification number (PIN). The PIN, which incorporates the date of birth, is unique to every Nordic citizen and permits accurate linkage of information among population and health registers. Detailed laboratory analyses are being conducted as an adjuvant to this epidemiologic study, and, to date, we have obtained biologic specimens for 41 of the 56 patients and have characterized the ATM mutations in 40 (21).

Estimation of Carrier Frequency

The frequency of being a carrier of a mutated ATM gene was estimated separately for each country by use of the Hardy-Weinberg equilibrium method. The possibility of early lethality in ATM homozygotes, however, was not taken into account. The number of affected individuals was taken from our epidemiologic study for the years from 1975 through 1995, and the number of infants born alive during the same years was obtained from the national statistics of each country.

Identification of Relatives

We sought to identify the parents of all of the A-T patients, who are obligate ATM heterozygotes; their siblings, who have a .67 probability of carrying a mutant ATM allele; their grandparents and biologic uncles and aunts, who have a .50 probability of carrying a mutant allele; and their great-grandparents, their grandparents' siblings, and their cousins, who have a .25 probability of carrying a mutant allele (Table 2). Pedigrees were constructed on the basis of data from the computerized national civil registration systems of the Nordic countries, supplemented with a so-called second generation registry in Sweden. These systems began in 1960 in Norway, in 1961 in Sweden, in 1967 in Finland, and

in 1968 in Denmark. They make use of a unique PIN, which was assigned to all citizens alive at the start of the respective system. For individuals born after that date, the PIN was assigned at birth. The PIN incorporates sex and date of birth and permits accurate linkage of registry information.

The identification of relatives of patients with A-T followed a similar procedure in each country because a direct cross-reference between parents and their offspring exists in all of these registration systems. Thus, by use of the PIN for all of the A-T patients (except two from Denmark who died before 1968), the patients' parents, grandparents, and great-grandparents were identified by full name and PIN so long as they were alive at the date of the inception of the national civil registration system. Subsequently, linkage of the PIN of each female relative in direct line with the national civil registration system identified siblings, uncles, aunts, cousins, and grandparents' siblings of the A-T patient (Table 2). In Denmark, Finland, and Norway, an additional manual search was made in the local population and church registers for all relatives of patients with A-T not alive at the date of inception of the respective national registration system and for relatives of the remaining two Danish A-T patients who had died before that date. In addition, we obtained follow-up information on date of death or emigration, if applicable, of patients and their relatives. Initially, the pedigrees of some of the Norwegian families were constructed from interviews with parents and other close relatives of A-T patients, but the pedigrees were subsequently reconstructed in more detail along the lines described above. Because of the particular design of the respective register facilities, we were unable to use record linkage to trace the grandparents' siblings in the Danish families, the cousins in the Norwegian families, and the great-grandparents and grandparents' siblings in the Swedish families.

A total of 1336 blood relatives were identified; their distribution by type of familial relationship and theoretical probability of being an ATM gene mutation carrier are shown in Table 2. Eight of the 76 siblings of the patients were half-siblings, as were nine of the parents' siblings (i.e., the uncles and aunts of the patients). In five families, the parents of the A-T patient were first cousins. The theoretical probability of being an ATM mutation carrier used in the analyses of cancer risk was adjusted appropriately for these families, including assigning the background probability ($\sim .005$ or 0.5%) of carrying an ATM mutation to blood relatives who married into consanguineous families, on the assumption that both mutations in the affected A-T patient were identical by descent as a result of the consanguinity.

Identification of Cancer in Patients and Relatives

Data on the A-T patients and their relatives were linked with the national cancer registry in the respective Nordic countries by the subjects' PINs or, if they had died before the civil registration systems were computerized, their date of birth, date of death (obtained from national mortality files), and name (22). The

Table 1. Clinical criteria fulfilled by 56 patients with ataxia-telangiectasia (A-T) included in the collaborative Nordic A-T study*

Criteria	No. of patients with symptoms/No. of patients for whom this information was available				
	Denmark (n = 19†)	Finland (n = 6)	Norway (n = 16)	Sweden (n = 15)	All (n = 56)
Absolute criterion, progressive cerebellar ataxia	19/19	6/6	16/16	15/15	56/56
Supporting criteria					
A-T	16/18	5/5	9/9	14/15	44/47
Ocular apraxia	16/18	5/6	6/6	12/14	39/44
Dysarthria	14/16	6/6	NA	12/13	32/35
History of infections‡	13/17	2/6	3/3	11/15	29/41
Elevated α -fetoprotein	5/5	6/6	6/7	8/9	25/27
Chromosome rearrangement involving chromosomes 7 and 14 or increased chromosomal breakage	9/11	3/5	NA‡	9/10	21/26
Decreased IgA or IgG2	16/18	1/6	6/7	5§/13 1 /14	—¶
Patient deceased as of December 31, 1995	13/19	1/6	8/16	1/15	23/56

*NA = not available. IgA = immunoglobulin A; IgG2 = immunoglobulin G2.

†For one deceased patient, the information was based on personal communication with the clinician only; clinical files were not available.

‡At least one episode of pneumonia.

§IgA was decreased in five patients.

||IgG2 was decreased in 11 patients.

¶Not applicable.

Table 2. Familial relationship and ATM gene carrier probability of 1336 unaffected blood relatives* of the 56 patients with ataxia-telangiectasia (A-T) in the Nordic countries

Relationship/theoretical gene carrier probability	Patients and relatives†				
	Denmark	Finland	Norway	Sweden	All four countries
	Population size, 1990, millions				
	5.2	5.0	4.2	8.6	23.0
A-T patients	19	6	16	15	56‡
Families	17	6	14	13	50
All relatives	509	403§	387§	137	1336
Fathers/1.0	17 (17)	6¶ (6)	14¶ (14)	11 (13)	48 (50)
Mothers/1.0	17 (17)	6¶ (6)	14¶ (14)	13 (13)	50 (50)
Brothers/0.67	18#	6	11	5**	40
Sisters/0.67	12#	6	3	15**	36
Grandfathers/0.5	32 (34)	12 (12)	23 (28)	16 (26)	83 (100)
Grandmothers/0.5	32 (34)	12 (12)	19 (28)	16 (26)	79 (100)
Uncles in blood/0.5	45††	29	23	14	111
Aunts in blood/0.5	53††	34	17	10	114
Male cousins/0.25	107	66	NA	16	189
Female cousins/0.25	89	59	NA	21	169
Great-grandfathers/0.25	43 (65)	21 (23)	27 (55)	NA	91 (143)
Great-grandmothers/0.25	44 (65)	23 (23)	29 (55)	NA	96 (143)
Grandparents' brothers/0.25	NA	56	56	NA	112
Grandparents' sisters/0.25	NA	67	51	NA	118

*Of the 1336 identified blood relatives, 118 had died before the date of eligibility.

†The actual number of relatives, whenever predefined, is given in parentheses. NA = not available.

‡Six families had two affected siblings with A-T.

§Family members deceased before 1953 were not included.

||Three pairs of parents were cousins in blood.

¶One pair of parents was cousins in blood.

#Five half-sibs to A-T patients.

**Three half-sibs to A-T patients.

††Nine half-sibs to parents of A-T patients.

period of follow-up for the occurrence of cancer among the A-T patients and their siblings, cousins, uncles, aunts, and grandparents' siblings extended from their date of birth or the date of inception of national cancer registration (1943 in Denmark, 1953 in Norway, 1953 in Finland, and 1958 in Sweden), whichever came last, up to the date of death or emigration or December 31, 1995, whichever came first. Similar rules were applied to the parents, grandparents, and great-grandparents of the A-T patients, except that follow-up was started at the earliest from the date of birth of the individual who is in direct line to the A-T patient (i.e., the date of birth of the parent of the A-T patient for the grandparent, etc.). Of the 1336 identified blood relatives, 118 had died before the date of eligibility, leaving 1218 relatives for analysis.

The malignant neoplasms identified in the study subjects were classified according to the International Classification of Diseases, 7th Revision (23). The registration and coding practices of the four cancer registries have been described elsewhere (24). Clinical details about the hematologic cancers identified in A-T patients and the breast cancers in their relatives, obtained from the notification forms of the cancer registries, were supplemented by information from the original histopathologic descriptions.

Written informed consent was obtained from each patient or from one of the parents in case of a child. The investigators were approved by the institutional review board of the Institute of Cancer Epidemiology, Copenhagen, Denmark.

Statistical Analysis

National incidence rates for the tumor categories were calculated according to sex, age (in 5-year groups), and 5-year calendar periods and applied to the person-years of observation in the respective national subcohorts to obtain the number of cancers expected. The observed and expected numbers of cancers, stratified by type of familial relationship and probability of carrying a mutation in the ATM gene, were pooled across country borders, and the standardized incidence ratios (SIRs) were calculated. The 95% confidence intervals (CIs) for

the SIRs were calculated by assuming a Poisson distribution of the observed cancers (25). The median age at death was estimated by use of the Kaplan-Meier method (26). All statistical tests were two-sided.

RESULTS

A carrier is a person with one wild-type and one mutated copy of the ATM gene. On the basis of the number of affected individuals of each country and the number of infants born alive, we estimated the ATM carrier frequency to be one of 183 in Denmark, one of 280 in Finland, one of 197 in Norway, and one of 210 in Sweden. Overall, we estimate that one of 220 (or 0.5%) persons in the Nordic countries are heterozygous carriers of a mutant allele of the ATM gene.

Cancers in A-T Patients

Twenty-three A-T patients had died by the end of follow-up (December 31, 1995), and the median age at death was 22.3 years (range, 5-38 years). On December 31, 1995, the mean age of the 33 living patients with A-T was 14 years (range, 0.6-31 years). The 56 A-T patients (23 males and 33 females; median year of birth, 1977; range, 1949-1995) had accrued a total of 893 person-years of follow-up (mean, 16 years; range, 0.6-38 years) during which time six cancers had developed, with 0.16 expected, yielding a highly significantly increased SIR of 37 (95% CI = 13 to 80). The malignancies all belonged to the main diagnostic group of cancers of the lymphatic and hematopoietic

tissues (four leukemias of the lymphoid subtype at the ages of 2, 6, 7, and 17 years and two solitary malignant lymphomas, one of the ileum and one of the tonsils, both diagnosed at the age of 13 years), with 0.05 cases expected (Table 3). No other cancer was observed among the A-T patients, compared with 0.10 expected. Of the 893 person-years at risk, 363 were accumulated during adulthood (defined as ≥ 20 years), which corresponds to an expected number of 0.04 cancers at all sites combined, including the breast.

Cancers in Blood Relatives

The 1218 blood relatives (609 males and 609 females; median year of birth, 1944; range, 1858–1995) represented some 34 000 person-years of follow-up (mean, 28 years; range, >0–53 years), during which time a total of 150 cancers were observed, with 126 expected, yielding a statistically significant increase in overall risk (SIR = 1.19; 95% CI = 1.01 to 1.40; Table 4). Of the 150 cancers, 21 were cancers of the breast, corresponding to an SIR of 1.53 (95% CI = 0.95 to 2.34); the SIR for cancers at all other sites combined was 1.15 (95% CI = 0.96 to 1.37). Subgroup analyses revealed no remarkable patterns of any other site-specific category of cancer; in particular, the rates of cancers of the lymphatic and hematopoietic tissues were similar to those of the background population (SIR = 0.8; 95% CI = 0.3 to 1.7; Table 4).

An excess of breast cancer was seen among female relatives in all countries except Sweden (Table 5). The risk of breast cancer, however, was statistically significantly increased only for the mothers of A-T patients (SIR = 7.1; 95% CI = 2.3 to 17), on the basis of five histologically confirmed invasive tumors. Sequence analyses of blood samples available from four of the five mothers showed no evidence of alterations in BRCA1 or BRCA2, mutations in which genes increase the risk of breast cancer. The risk of breast cancer in other female relatives was not statistically significantly increased (SIR = 1.2; 95% CI = 0.7 to 2.0). When all obligate female gene carriers (seven grandmothers from the consanguineous families and all 50 mothers) were considered together, this group was at a statistically significantly increased risk of breast cancer (SIR = 4.7; 95% CI = 1.5 to 11) due entirely to the five cases among the mothers (Table 5). No tendency for increasing risk of breast cancer with increasing probability of being a carrier was seen in the remaining groups of female relatives defined by their probability of A-T heterozygosity (0.67, 0.50, 0.25, or background) (Table 5). Six cancers at sites other than the breast were observed among the 108 female and male obligate carriers in the study, with 5.7

cases expected (SIR = 1.05; 95% CI = 0.4 to 2.2) (not shown in table).

If the theoretical probability of being an ATM carrier is multiplied by the number of subjects in each subgroup of female

Table 4. SIRs for cancer in 1218 relatives of 56 patients with ataxia-telangiectasia in the Nordic countries*

Site of cancer (ICD-7 classification)	Obs	Exp	SIR (95% CI)
All malignant neoplasms (140–204)	150	126.03	1.19 (1.01 to 1.40)
Breast (170)	21	13.72	1.53 (0.95 to 2.34)
Female (170)	21	13.62	1.54 (0.95 to 2.36)
Male (170)	0	0.10	0.00 (0.0 to 37)
Other sites combined	129	112.31	1.15 (0.96 to 1.37)
Digestive organs	43	34.0	1.3 (0.9 to 1.7)
Stomach (151)	15	10.1	1.5 (0.8 to 2.4)
Colon/rectum (153–154)	17	15.1	1.1 (0.6 to 1.8)
Other digestive organs (150, 152, 155–159)	11	8.8	1.3 (0.6 to 2.3)
Respiratory system (160–164)	18	14.3	1.2 (0.7 to 1.9)
Female genital organs (171–176)	14	11.0	1.3 (0.7 to 2.1)
Male genital organs (177–179)	12	11.5	1.0 (0.5 to 1.8)
Urinary tract (180–181)	8	9.0	0.9 (0.4 to 1.8)
Melanoma of skin (190)	4	3.0	1.3 (0.4 to 3.4)
Other skin† (191)	6	7.0	0.9 (0.3 to 1.9)
Lymphatic and hematopoietic tissues (200–204)	7	8.5	0.8 (0.3 to 1.7)
Non-Hodgkin's lymphoma (200, 202)	3	2.4	1.3 (0.3 to 3.7)
Multiple myeloma (203)	1	1.8	0.6 (0.0 to 3.1)
Leukemia (204)	3	3.2	0.9 (0.2 to 2.7)

*SIR = standardized incidence ratio; ICD-7 = International Classification of Diseases, 7th Revision (23); Obs = observed cancers; Exp = expected cancers; CI = confidence interval.

†Includes squamous cell carcinomas of the skin and, in Denmark, basal cell carcinomas.

Table 5. SIRs for breast cancer in female relatives by country, familial relationship, and probability of carrying an ATM mutation*

Subgroup of female relatives	No.	Person-years at risk	Breast cancer		
			Obs	Exp	SIR (95% CI)
Total	609	17 519	21	13.62	1.53 (0.95 to 2.34)
Country					
Denmark	239	6930	6	4.52	1.3 (0.5 to 2.9)
Finland	161	4577	6	3.18	1.9 (0.7 to 4.1)
Norway	134	4305	8	4.94	1.6 (0.7 to 3.2)
Sweden	75	1707	1	0.98	1.0 (0.0 to 5.7)
Familial relationship					
Mother	50	899	5	0.70	7.1 (2.3 to 17)
Sister	35	672	0	0.01	0.0 (0.0 to 2.5)
Grandmother	78	2603	5	3.30	1.5 (0.5 to 3.5)
Aunt	110	4476	0	2.00	0.0 (0.0 to 1.9)
Great-grandmother	72	1799	5	3.00	1.7 (0.6 to 4.0)
Grandparents' sister	100	3350	6	4.30	1.4 (0.5 to 3.0)
Female cousin	164	3720	0	0.34	0.0 (0.0 to 11)
Theoretical gene carrier probability					
1	57	1176	5	1.07	4.7 (1.5 to 11)
0.67	31	601	0	0.01	0.0 (0.0 to 258)
0.50	178	6644	5	4.84	1.0 (0.3 to 2.4)
0.25	335	8936	11	7.42	1.5 (0.7 to 2.7)
Background†	8	162	0	0.28	0.0 (0.0 to 13)

*SIR = standardized incidence ratio; Obs = observed cancers; Exp = expected cancers; CI = confidence interval.

†Frequency in the general population, i.e., approximately 0.005. Relatives who married into consanguineous families.

Table 3. SIRs for cancer in 56 patients with ataxia-telangiectasia in the Nordic countries*

Site of cancer (ICD-7 classification)	Obs	Exp	SIR (95% CI)
All malignant neoplasms (140–204)	6	0.16	37 (13 to 80)
Lymphatic and hematopoietic tissues (200–204)	6	0.05	113 (41 to 246)
Non-Hodgkin's lymphoma (200, 202)	2	0.01	244 (27 to 880)
Hodgkin's disease (201)	0	0.01	0 (0 to 369)
Leukemia (204)	4	0.03	120 (36 to 341)
Other sites combined (140–199)	0	0.10	0 (0 to 37)

*SIR = standardized incidence ratio; ICD-7 = International Classification of Diseases, 7th Revision (23); Obs = observed cancers; Exp = expected cancers; CI = confidence interval.

relatives (see also bottom of Table 5), the number of actual gene carriers can be estimated to be 251 of the 609 female relatives included in the risk analysis, i.e., 41%. Similarly, if the gene carrier probabilities are applied to the expected figures for breast cancer in Table 5, we should expect, on the basis of national breast cancer rates, to see 5.35 breast cancers among the 251 female gene carriers. Furthermore, if we assume that the excess of 7.38 breast cancers found among all female relatives (21 breast cancers observed: 13.62 expected) can be ascribed to the 251 gene carriers, the relative risk for female breast cancer associated with heterozygosity for A-T can be estimated roughly as $(7.38 + 5.35)/5.35$, or 2.38 (95% CI = 1.25 to 4.11). It follows that the excess cumulative number of 7.38 breast cancers among 251 carriers is equivalent to an excess prevalence of breast cancer among heterozygous ATM gene mutation carriers of approximately 7.38/251, or 3%.

Breast Cancer Risk Modification by Age

The average age at diagnosis of breast cancer in the 21 female relatives was 52 years (range, 38–79 years), reflecting, in part, the relatively young age of this population. On the basis of the usual 5-year age categories, we observed a 2.5-fold to threefold increase in risk of breast cancer up to the age of 55 years relative to the general female population (Table 6), although none of the age-specific SIR estimates reached statistical significance. For women over the age of 55 years, the excess risk seemed to disappear gradually. Guided by the observed relative risk pattern, we analyzed broader age groups and found SIRs of 2.6 (95% CI = 1.4 to 4.4) for women below the age of 55 years and 0.9 (95% CI = 0.4–1.8) for women aged 55 years or older. In a further analysis in which the type of relationship was specified, we found a tendency for breast cancer to be increased at a young age among grandmothers, great-grandmothers, grandparents' sisters, and, in particular, mothers (Table 7). However, the age-specific subgroup analysis of Table 7 was a *post hoc* evaluation of data and should be looked on as exploratory.

Cancer Risk by Consanguinity

Separate analyses of the cancer risks of 185 relatives of the A-T patients from the five consanguineous families, that is, those in which the parents of the A-T patient were first cousins,

Table 6. SIRs for breast cancer in female relatives by age at diagnosis in six age groups chosen prior to the analysis and two age groups chosen after the analysis*

Age, y	Age at breast cancer diagnosis†					
	A priori			A posteriori‡		
	Obs	Exp	SIR (95% CI)	Obs	Exp	SIR (95% CI)
<40	2	0.82	2.4 (0.3 to 8.8)			
40–44	3	1.05	2.8 (0.6 to 8.3)			
45–49	4	1.64	2.4 (0.7 to 6.3)			
50–54	4	1.57	2.6 (0.7 to 6.5)			
<55				13	5.08	2.6 (1.4 to 4.4)
≥55				8	8.54	0.9 (0.4 to 1.8)
55–59	3	1.61	1.9 (0.4 to 5.4)			
≥60	5	6.93	0.7 (0.2 to 1.7)			

*SIR = standardized incidence ratio; Obs = observed cancers; Exp = expected cancers; CI = confidence interval.

†Categorization was guided by the observed risk estimates of the 5-year age groups.

Table 7. SIRs for breast cancer in female relatives by age at diagnosis, familial relationship, and ATM gene carrier probability*

Female relatives	Age at breast cancer diagnosis†					
	<55 y			≥55 y		
	Obs	Exp	SIR (95% CI)	Obs	Exp	SIR (95% CI)
Total	13	5.08	2.6 (1.4 to 4.4)	8	8.54	0.9 (0.4 to 1.8)
Familial relation						
Mother	5	0.59	8.5 (2.7 to 20)	0	0.11	0.0 (0.0 to 37)
Sister	0	0.01	0.0 (0.0 to 369)	—	—	—
Grandmother	3	1.30	2.3 (0.5 to 6.7)	2	2.00	1.0 (0.1 to 3.6)
Aunt	0	1.40	0.0 (0.0 to 2.6)	0	0.60	0.0 (0.0 to 6.5)
Great-grandmother	1	0.40	2.5 (0.0 to 14)	4	2.56	1.6 (0.4 to 4.0)
Grandparents' sister	4	1.04	3.9 (1.0 to 9.9)	2	3.26	0.6 (0.1 to 2.2)
Female cousin	0	0.33	0.0 (0.0 to 12)	0	0.01	0.0 (0.0 to 369)
Carrier probability						
1	5	0.71	7.1 (2.3 to 17)	0	0.38	0.0 (0.0 to 10)
0.67	0	0.01	0.0 (0.0 to 369)	—	—	—
0.50	3	2.52	1.2 (0.2 to 3.5)	2	2.31	0.9 (0.1 to 3.1)
0.25	5	1.80	2.8 (0.9 to 6.5)	6	5.61	1.1 (0.4 to 2.3)
Background‡	0	0.04	0.0 (0.0 to 123)	0	0.24	0.0 (0.0 to 15)

*SIR = standardized incidence ratio; Obs = observed cancers; Exp = expected cancers; CI = confidence interval.

†Using *a posteriori* groupings (see Table 6).

‡Frequency in the general population, i.e., approximately 0.005.

showed 18 cancers at all sites, with 17.1 expected (SIR = 1.1; 95% CI = 0.6 to 1.7), and two breast cancers (diagnosed in women at the ages of 38 and 57 years), with 1.9 expected (SIR = 1.1; 95% CI = 0.1 to 3.9). Thus, in comparison with the equivalent relative risk estimates for the 45 nonconsanguineous families of 1.2 (95% CI = 1.0 to 1.4) and 1.6 (95% CI = 1.0 to 2.5), respectively, there was no tendency to higher risks for total cancer or breast cancer in consanguineous families (not shown in tables).

Cancer Risk by Cancer Status of the A-T Patients

A slight, statistically nonsignificant tendency was observed for a higher relative risk for cancer among the 150 relatives of the six A-T patients with cancer than among the 1068 relatives of A-T patients without cancer. In the former group, 33 cancers were observed at all sites combined, whereas 22.8 were expected (SIR = 1.5; 95% CI = 1.0 to 2.0); these included six breast cancers (diagnosed in women aged 38, 47, 49, 50, 57, and 79 years), with 2.6 expected (SIR = 2.3; 95% CI = 0.8 to 5.0). The equivalent SIR estimates for relatives of A-T patients without cancer were 1.1 (95% CI = 0.9 to 1.4) and 1.4 (95% CI = 0.8 to 2.2), respectively (not shown in tables).

DISCUSSION

Our follow-up of 1218 blood relatives of patients with A-T showed a modest, 50% increased risk of breast cancer among female relatives, on the basis of 21 observed cases. The increased breast cancer risk was seen mainly among mothers of children with A-T, based on five incident cases, but was not evident among other blood relatives. [Two cases had been reported previously (10), so our observation is not independent of these cases.] The risk of breast cancer associated with ATM heterozygosity was estimated to be 2.4 times that of the general female population, with a lower 95% CI of 1.3, based on an analysis adjusting for the probability of specific subgroups of

female relatives being ATM gene mutation carriers. The equivalent relative risk estimate for all relatives assumed to be obligate carriers (i.e., the mothers of the A-T patients and the seven identified grandmothers in the consanguineous families) was 4.7, with a lower 95% CI of 1.5. Thus, the findings in obligate carriers are consistent with the hypothesis that heterozygous carriers of an ATM mutation have an increased risk of breast cancer and are in general agreement with the relative risk estimates of breast cancer found in previous epidemiologic investigations (6-12,15).

On the other hand, our data do not provide entirely convincing evidence that heterozygous carriers are at increased risk of breast cancer because we did not observe a trend of increasing risk for breast cancer with each increment in the theoretical probability of being an ATM gene mutation carrier. The lack of such a trend tempers the causal interpretation of our finding and raises questions as to the likelihood of a simple genetic link. Of interest, a recent study in France of 1429 blood relatives in 42 families of A-T patients (11) found a similar pattern, with a 3.3-fold increased risk for breast cancer in obligate carriers but no consistent trend in the risk in other female relatives grouped by probability of carrying an ATM mutation, based on a total of 28 breast cancer cases. In addition, a recent study of cancer mortality in the U.K. of the parents and grandparents of 95 patients with A-T (12) also showed the same peculiar pattern, with a 3.3-fold higher risk for breast cancer among obligate carriers (mothers) than in the national female population but a relative risk of 0.9 for the 50% gene carrier group (grandmothers). The lack in our study of "dose-response" with inferred genotype may be clarified with actual genotyping of family members, but the numbers of informative relatives will be much smaller and the risk estimates more unstable. The absence of BRCA1/2 mutations in the mothers also makes it unlikely that an interaction between mutations in one of these genes and ATM (27) explain the relative risks we observed. Finally, our observations that the risk of breast cancer is not increased in consanguineous families and that it is increased in families in which the A-T patients developed cancer are not easily interpreted, although it seems unlikely that breast cancer in both of these families would be due to a simple, one-gene association with heterozygosity for ATM.

The excess risk of breast cancer among the mothers is so large that confounding is an unlikely explanation. Confounding would, for example, be possible if this group were less likely than the general population to have children or more likely to have children later in life (28). However, the reproductive pattern in the 50 families under study indicates that neither factor is of any importance. To the contrary, we may have underestimated the strength of the association in female blood relatives in direct line with the A-T patient (mothers, grandmothers, and great-grandmothers), because the national rates for breast cancer are influenced by an approximately 30% higher risk of breast cancer among nulliparous women than among parous women. Confounding could also arise if cases of A-T were more precisely diagnosed in children of mothers who later develop a breast cancer; however, this possibility is unlikely because this is a record linkage study. Finally, although we have no evidence to suspect a bias in our population-based study, one might have occurred if mothers of children with A-T were more likely to receive special screening examinations for the early detection of breast cancer than the general population, perhaps because cli-

nicians have now become aware of the purported link between ATM heterozygosity and breast cancer.

An alternative hypothesis for the absence of a gradient of breast cancer incidence above background levels between sisters, aunts, and cousins and for the finding of an increased incidence confined to mothers might be that giving birth to an A-T child has an effect on the mother's breast cancer risk in combination with or regardless of any effect of her ATM heterozygosity.

Although the ATM carrier frequency of 0.5% in the Nordic populations is remarkably similar to that reported in the United States among women with early-onset breast cancer (<40 years) and matched control subjects (18), we may have overestimated it somewhat. Five of the 56 affected individuals were born to families in which the parents were cousins; in addition, in some sparsely populated areas in Finland, Norway (29), and northern Sweden, there may have been excess inbreeding, which would exaggerate the carrier frequency estimates (30). Nevertheless, on the basis of our estimated carrier frequency and the relative risk estimates derived from the study groups in the present investigation, we estimate an excess prevalence of breast cancer among heterozygous ATM mutation carriers of approximately 3%. Although some of the women in our study were not followed throughout their lives, this figure would be approximately equivalent to the oncogenic penetrance of mutations in this gene, assuming that the association is causal. On the basis of this estimate, it follows that approximately 200 breast cancers annually in the Nordic female population (which numbers around 12 million in total) might be attributable to ATM heterozygosity, which is equivalent to 1.4% of the 14 600 cases diagnosed annually at all ages combined.

Although the epidemiologic studies point to a threefold to fourfold increased risk of breast cancer among ATM carriers, mutational analyses of the ATM gene provide little support for this conclusion (31). Many, if not all, laboratory investigations have found no increase in the frequency of ATM mutations among women with breast cancer (16-20), including early-onset breast cancer (18), sporadic breast cancer (19,20), and familial breast cancer (16,17). One explanation for this apparent conflict might be that the molecular studies have looked for the presence of only a small number of known mutations in limited study populations, whereas the epidemiologic studies have involved only a small number of breast cancers (13). Because of these methodologic limitations, coupled with the apparent low prevalence of ATM gene mutations in the general population and the relative rarity of breast cancer, even among ATM heterozygotes, the apparent conflicting evidence is not necessarily inconsistent (14,32). An attempt has recently been made to reconcile the epidemiology with the mutational analyses in terms of differences in the types of mutations prevalent in families and the general population (32), but such differences in the types of mutations found in familial A-T versus general population studies have yet to be demonstrated.

It is noteworthy that an excess of cancers, other than female breast cancer, was not evident among the relatives of the A-T patients in our study. This observation is consistent with some (9,10,12) but not all (6,7) previous studies. The reasons for these differences among studies are not entirely clear, but they may be related to the influences of selection biases, reporting practices, or features of study follow-up. Although we evaluated a relatively small number of A-T patients, i.e., 56 of 50 families, we

found a high risk of leukemia and lymphoma, consistent with previous understanding (5). In contrast, among the more than 1200 blood relatives in our study, no excess risk of leukemia or lymphoma was found, and risks greater than 1.7-fold could be excluded with 95% confidence. Although a recent study (33) suggests that ATM mutations may be increased in patients with B-cell chronic lymphocytic leukemia, our data do not suggest that germline mutations in the ATM gene are responsible for increased cancer susceptibility among heterozygotes, with the possible exception of female breast cancer.

The unique features of our study include unbiased identification of relatives through population registry linkage, unbiased ascertainment and validation of cancer through cancer registry linkage, and nearly complete follow-up of the entire study population. Despite these study strengths, the number of breast cancers identified was not large, and it was surprising that breast cancer risk was increased only among mothers and not among other blood relatives. Overall, however, our data do provide some support for the hypothesis of a link between heterozygosity for a mutant ATM allele and an increased incidence of female breast cancer. If the link is indeed causal, our data further indicate that the oncogenic penetrance of the mutated ATM gene in its heterozygote state is low, i.e., likely of the order of 3% in a lifetime. The population attributable risk associated with a damaged ATM gene would, therefore, be closer to 1%–2% than to the previously estimated 6%–8% (6,15).

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NOTES

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